APPENDIX B

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WILLIAM G. GOSZ

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WILLIAM G. GOSZ
GENZYME CORP.
ONE KENDALL SQ.
CAMBRIDGE, MA 02139

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☒ This application has been examined ☒ Responsive to communication filed on 2/20/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), ---- days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9 and 11 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-9 and 11 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The application should be reviewed for errors.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-3, 5-9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to a DNA sequence comprising a whey acidic protein promoter. See MPEP 706.03(n) and 706.03(z).

The specification is not enabling for a DNA sequence comprising all milk protein promoters. While the claims are directed to the use of all milk protein promoters, the specification only discloses the construction of fusion genes using a single milk protein promoter (whey acidic protein promoter). However, it is well known in the art that the level and the mode of expression of each transgene as well as the effects of its expression on the animal as a whole are not readily predictable due to uncontrollable factors such as the site of integration of the transgene. There is insufficient evidence in the specification which indicates that all milk protein promoters can be utilized with success for the expression of a heterologous polypeptide in a transgenic mammal without undue experimentation. There is also no disclosure on the preparation of a DNA sequence comprising a casein promoter or other milk serum protein promoters. Accordingly, the disclosure is enabling only for claims limited to a DNA sequence comprising a whey acidic protein promoter.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-4 and 6-9 are rejected under 35 U.S.C. 103 as being unpatentable over Andres et al..

Andres et al. disclose a DNA construct comprising the human H-ras gene operably linked to the whey acidic protein promoter. Their teachings differ from the claimed invention in that the DNA construct does not further comprise the whey acidic protein signal sequence enabling secretion of the human H-ras protein. However, it would have been obvious for one of ordinary skill in the art to modify the DNA construct taught by Andres et al. by inserting into the construct the whey acidic protein signal sequence for the expected benefit of obtaining secretion of the human H-ras protein into milk, with a reasonable expectation of success. Thus the claimed invention

as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claims 5 and 11 are rejected under 35 U.S.C. 103 as being unpatentable over Andres et al., as applied to claims 1-4 and 6-9 above, and further in view of Pennica et al. or Chisari et al..

Pennica et al. disclose a cDNA encoding human tissue plasminogen activator (tPA) and its expression in E. coli while Chisari et al. disclose a DNA segment encoding the hepatitis B surface antigen (HBsAg) and its expression in transgenic mice. Accordingly, the additional modification of the DNA construct taught by Andres et al. by substituting the DNA encoding human tPA or HBsAg (each containing its own signal sequence for secretion) for the human H-ras gene would have been obvious to one of ordinary skill in the art. Thus the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claims 1-9 and 11 are rejected under 35 U.S.C. 103 as being unpatentable over Campbell et al., when taken with either Pennica et al. or Chisari et al., and further in view of any one of Palmiter et al., Ross et al. or Stewart et al..

Campbell et al. disclose the genes coding for the rat and mouse mammary tissue-specific whey acidic protein and their promoter regions. They do not specifically teach a DNA construct comprising a whey acidic protein promoter operably linked to a DNA sequence encoding a heterologous protein such as human tPA or HBsAg. However, at the time the claimed invention was made, Pennica et al. disclosed a cDNA encoding human tPA while Chisari et al. disclosed a DNA segment encoding HBsAg. Furthermore, Palmiter et al. reviewed the many studies on the tissue-specific expression of heterologous gene products in transgenic mice while Ross et al. and Stewart et al. each reported mammary tissue-specific expression of heterologous genes in transgenic mice. Accordingly, it would

have been obvious for one of ordinary skill in the art to operably link the whey acidic protein promoter to a DNA sequence encoding human tPA or HBsAg in order to obtain a DNA construct useful for the expression and secretion of human tPA or HBsAg in the mammary tissue of a transgenic mammal, with a reasonable expectation of success. Thus the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Copies of some of the cited art were provided with parent application SN 07/441,785.

No claim is allowed.

Any inquiry concerning this communication should be directed to Jasemine C. Chambers, Ph. D., at telephone number (703) 308-2035.

Jasemine C. Chambers

JASEMINE C. CHAMBERS
PRIMARY EXAMINER
GROUP 1800